A Genomic Approach to Elucidate the Molecular Mechanisms Underlying Manganese Neurotoxicity

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Background: Manganese is widely present in the environment, and manganese exposures may lead to its accumulation in the brain, causing serious neurotoxicity. Exposure of adult humans to manganese has long been known to cause neurotoxicity. Recent evidence also suggests that exposure of children to manganese is associated with developmental neurotoxicity. Thus, understanding the molecular mechanisms underlying manganese neurotoxicity should help assess and prevent the adverse health effects of manganese on humans. To elucidate the key potential mechanisms underlying manganese neurotoxicity, we applied a genomic approach to identify all molecular targets of manganese in primary human neural cells.

Methods: Primary human fetal astrocytes were exposed to manganese chloride for up to one week. Microarray gene expression profiling was performed to detect the transcript levels of all human genes and identify all potential manganese targets. Then, various techniques of biochemistry and cell biology were applied to confirm the effects of manganese on transcript and protein levels of important genes and on astrocytic cell cycle progression.

Results: Manganese exposure increased the transcript and protein levels of 28 genes encoding proinflammatory mediators, but it decreased the expression levels of 15 genes encoding functions involved in DNA replication and repair and cell cycle checkpoint control. Consistent with its effect on gene expression, manganese also caused astrocytes to accumulate in the S phase of cell cycle.

Conclusions: Inflammatory activation of astrocytes, increased expression of proinflammatory mediators, and activation of related signaling pathways might be important mechanisms leading to manganese neurotoxicity.

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